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# Oral forms of secondary syphilis: An illustration of the pitfalls set by the great imitator



Alexandre Lampros, MD,<sup>a,b</sup> Vannina Seta, MD,<sup>a</sup> Phillippe Gerhardt, MD,<sup>c</sup> Camille Isnard, MD,<sup>a</sup> Corinne Husson, MD,<sup>d</sup> and Nicolas Dupin, MD<sup>a,c,e,f</sup>  
Paris, France

**Introduction:** Syphilis is reemerging in certain populations, such as in men who have sex with men in particular. Oral manifestations are not uncommon and can render diagnosis difficult, particularly if occurring in isolation.

**Materials and methods:** We recovered clinical data for all patients receiving a diagnosis of secondary syphilis who were referred to the National Reference Center for Syphilis in Paris, France, from January 2000 to July 2019. We selected patients presenting oral symptoms only and analyzed their general characteristics, time to diagnosis, and clinical presentations.

**Results:** Secondary syphilis was diagnosed in 206 patients, 38 of whom (18%) presented oral manifestations, which were isolated in 14 patients (37%). The main oral manifestations were subacute erosive or ulcerative lesions (55%), mucous patches on the tongue (53%), and nodular (10%) and leukokeratotic lesions (5%). Mean time to diagnosis was 4.5 months, but was significantly longer for patients with isolated oral symptoms (8.8 vs 1.8 months;  $P = .02$ ).

**Conclusion:** Oral presentations of secondary syphilis are frequent and challenging for diagnosis, even in patients with epidemiologic risk factors. Clinicians confronted with subacute oral lesions in such patients should bear in mind the possibility of this contagious, curable, and sometimes severe disease. (J Am Acad Dermatol 2021;84:348-53.)

**Key words:** dermatology; men who have sex with men; oral mucosa; syphilis; *Treponema pallidum*.

## INTRODUCTION

Syphilis is an infectious disease caused by the spirochete *Treponema pallidum* subsp *pallidum*. It is transmitted by sexual contact or exposure to contaminated blood through transfusion or pregnancy. The reservoir of syphilis is strictly human. This disease is therefore a good candidate for eradication, particularly because rapid diagnostic tests have been developed and there are usually no treatment difficulties. Nevertheless, syphilis remains a heavy public health burden, particularly in low-income countries, in which its prevalence is

highest.<sup>1</sup> The incidence of syphilis has increased during the last 20 years in high-income countries, particularly in men who have sex with men.<sup>2,3</sup>

Syphilis may manifest in diverse manners, rendering its diagnosis difficult and contributing to the persistence and spread of the disease. It may be classified as early syphilis (primary, secondary, and early latent disease of less than 1 year's duration) and late syphilis (late latent and tertiary disease). Secondary syphilis results from the systemic spread of the bacteria. It may affect any organ, but mostly presents with dermatologic, rheumatologic,

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From Service de Dermatologie, Hôpital Cochin, Assistance Publique des Hôpitaux, Paris<sup>a</sup>; Sorbone University, Paris<sup>b</sup>; CeGIDD, Hôpital Hôtel Dieu, Assistance Publique des Hôpitaux, Paris<sup>c</sup>; Cabinet Médical, Paris<sup>d</sup>; Centre National de Référence des infections sexuellement transmissibles, Laboratoire associé Syphilis<sup>e</sup>; and Institut Cochin, Inserm 1016, Université de Paris.<sup>f</sup>

Funding sources: None.

Conflicts of interest: None disclosed.

Accepted for publication April 17, 2020.

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Reprints not available from the authors.

Correspondence to: Nicolas Dupin, MD, Service de Dermatologie et CeGIDD, Hôpital Cochin, site Tarnier, 89 Rue d'Assas 75006 Paris, France. E-mail: [nicolas.dupin@aphp.fr](mailto:nicolas.dupin@aphp.fr).

Published online April 24, 2020.

0190-9622/\$36.00

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<https://doi.org/10.1016/j.jaad.2020.04.089>

neurologic, and ocular signs.<sup>4</sup> The spectrum of clinical manifestations associated with the secondary stage is very large, mimicking many other diseases. Oral mucosal manifestations are not uncommon at this stage and may be observed in isolation, contributing to delays in diagnosis.<sup>5</sup>

We present here a clinical description of 38 patients with oral manifestations of secondary syphilis. We aimed to highlight the diagnostic difficulties encountered and to distinguish different clinical phenotypes. By doing so, we aimed to increase the awareness of clinicians likely to encounter this disease in a clinical setting to facilitate earlier diagnosis of this transmissible and curable disease.

## MATERIALS AND METHODS

This study was conducted at the National Reference Center for Syphilis in Paris. We collected the available clinical data for patients with a diagnosis of secondary syphilis who presented with oral mucosal manifestations between January 2000 and July 2019. The patients enrolled gave informed consent for participation in the RésIST network and the GENOSYPH study.

Secondary syphilis was diagnosed on the basis of the 2015 Centers for Disease Control and Prevention criteria,<sup>6</sup> which include relevant clinical findings (essentially localized or diffuse mucocutaneous lesions) associated with double-positive serologic results for a treponemal assay (*T pallidum* particle agglutination assay, fluorescent treponemal antibody absorption, and enzyme immunoassay) and a nontreponemal assay (the venereal disease research laboratory test or the rapid plasma reagin test).

For each patient, we collected the available information for general characteristics (age, sex, and relevant medical history), sexually transmitted diseases risk factors (number of sexual partners per year, whether the patient was a man who had sex with men, HIV status, and history of other sexually transmitted diseases), data concerning the patient's medical history before final diagnosis (time to diagnosis, defined as time between the first oral signs and diagnosis; numbers of physicians

consulted; the differential diagnoses considered; treatments administered; and evaluations performed before diagnosis). We also noted the clinical manifestations, recording the oral and extraoral symptoms described in clinical files, when possible comparing them with photographs recovered from the files. We also considered the treatment administered and outcome.

In the statistical analysis, we compared time to diagnosis between patients with isolated and nonisolated oral manifestations, and between patients with and without HIV infection, in Mann-Whitney-Wilcoxon tests performed in R statistical software (version 3.5.3, R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

Between January 2000 and July 2019, 403 patients included prospectively in the GENOSYPH study conducted by the National Reference Center for Syphilis in France were treated in our dermatology department. These patients included 206 (51%) with a diagnosis of secondary syphilis, 38 (18%) of whom had oral manifestations, which were observed in isolation in 14 patients (7%) (Fig 1).

### Population characteristics and risk factors for sexually transmitted diseases

The study population consisted essentially of men (95%) aged 21 to 63 years (Table I). Most (98%) were men who had sex with men. Patients living with HIV accounted for approximately a third of the study population (37%). Most patients presented good immunovirologic disease control (CD4 lymphocyte counts >200/mm<sup>3</sup> and no viral load detected in 85%). A history of sexually transmitted diseases other than HIV was found in 20 patients (53%). The most frequently reported sexually transmitted diseases were hepatitis B (28%), gonorrhea (26%), and condylomas (23%).

### Data suggestive of diagnostic difficulties

The mean time from the first signs of oral secondary syphilis to diagnosis was 4 months (range 5 days to 2 years) and was significantly longer for patients presenting isolated oral manifestations (8.8 vs 1.7 months;  $P = .02$ ) (Fig 2) and shorter for

## CAPSULE SUMMARY

- Oral manifestations are not uncommon and can render diagnosis difficult, particularly if occurring in isolation in patients with secondary syphilis. Oral presentations of secondary syphilis are frequent and challenging for diagnosis, even in patients with epidemiologic risk factors.
- Clinicians confronted with subacute oral lesions in such patients should bear in mind the possibility of this contagious, curable, and sometimes severe disease. This article highlights that oral manifestations can be isolated and this may delay the diagnosis of secondary syphilis.

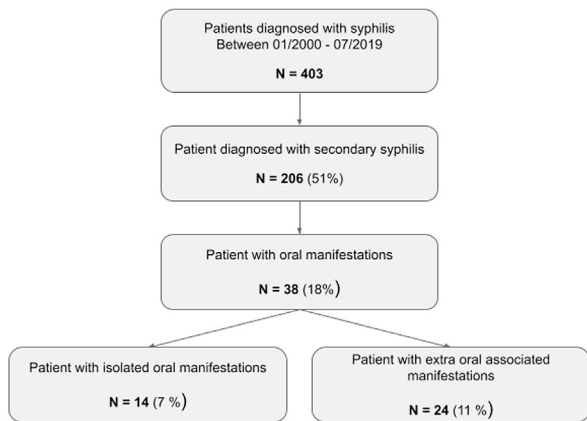


Fig 1. Flow chart of the study.

Table I. Population characteristics

Sociodemographic and clinical characteristics	All patients (n = 38), %	Isolated oral manifestations (n = 14), %	Nonisolated oral manifestations (n = 24), %
Mean age, y	39.9	41.9	38.8
Men	97	100	96
French origin	68	57	75
History of sexual transmitted diseases	53	43	58
Man who has sex with men	95	100	92
HIV positive	37	21	46
Mean time to diagnosis, mo	4.5	8.8	1.7
Presumptive treatment for alternative diagnosis	24	29	21
Biopsy performed	21	42	8
Erosive or ulcerative lesions	55	86	46
Mucous patches on the tongue	53	21	29
Nodular lesions	10	14	8
Leukokeratotic plaques	5	7	4
Associated lesions	24	26	21

patients living with HIV (1.5 vs 5.8 months;  $P = .06$ ) (Fig 3). We detected no trend suggestive of a decrease in this time from 2000 to 2019.

Most patients ( $n = 23$ ; 60%) consulted more than 1 practitioner (median 2) before being referred to our center for sexually transmitted disease. No testing for syphilis was performed at the first clinical presentation in 76% of patients ( $n = 29$ ). The main

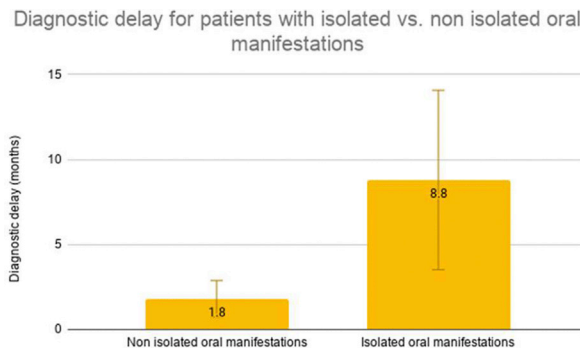


Fig 2. Comparison of time for diagnosis for patients with isolated oral manifestations versus those with nonisolated ones during secondary syphilis.

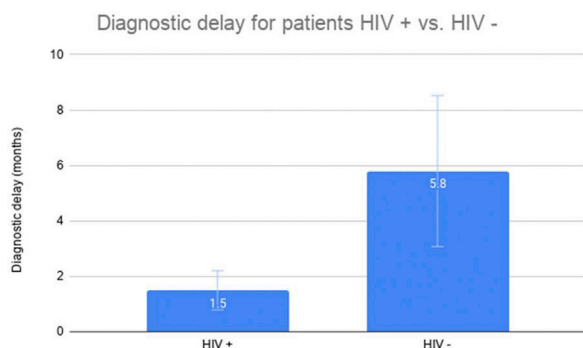


Fig 3. Comparison of time for diagnosis for HIV-positive patients versus HIV-negative ones.

differential diagnoses considered were viral, fungal, and dental infections; oral tumors; gastric acid reflux; urticaria; pemphigus; and lupus. This led to presumptive treatment (antiviral drugs, antifungal agents, antibiotics, and antihistamines) in 24% of patients ( $n = 9$ ). A biopsy was performed on isolated oral lesions in 21% of cases ( $n = 8$ ).

Clinical description of oral and associated extraoral manifestations

**Oral manifestations.** We identified 2 main clinical phenotypes of oral manifestations that appeared to be of particular relevance in our population: erosive (Fig 4) or ulcerative mucosal lesions and mucous patches on the tongue. We considered angular mucositis (Fig 5, A) a specific location of erosive or ulcerative lesions. The other forms encountered were leukokeratotic plaques (5%;  $n = 2$ ) and nodular lesions (10%;  $n = 4$ ) (Fig 6). Erosive or ulcerative lesions were found in 21 patients (55%) (Fig 7) at various locations (lingual mucosa 56%,  $n = 12$ ; angular mucositis 25%,  $n = 5$ ; palatine mucosa 25%,  $n = 5$ ; labial mucosa 17%,  $n = 4$ ; jugal mucosa 17%,  $n = 4$ ; and gingival mucosa 8%;  $n = 2$ ). Lingual erosive and ulcerative lesions were



**Fig 4.** Well-delimited erosive erythematous macula of the upper lip.

observed mostly at lateral positions (70%;  $n = 12$ ). Multiple sites were involved in most cases (65%;  $n = 10$ ).

Mucous patches were observed on the tongue in 20 patients (53%). Erosive lesions and mucous patches were observed together in only 4 cases (11%); all 3 patients with nodular lesions had associated erosive or ulcerative lesions. Leukokeratotic plaques were observed only in isolation. They were considered specific because they disappeared after treatment.

#### **Patients with isolated oral manifestations**

As reported earlier, isolated oral symptoms were observed in 14 patients (37% of our cases) and were associated with a significantly longer time to diagnosis. Erosive or ulcerative lesions were the predominant form observed in these patients (12/14; 86%). They occurred at a much higher frequency than mucous patches on the tongue, which were observed in only 3 of 14 patients (21%). The proportions of isolated forms were similar in the HIV and non-HIV groups (50% and 58%, respectively).

#### **Patients with extraoral manifestations**

Extraoral manifestations were noted in 24 of 38 patients (63%). They mostly involved the skin and anal and genital mucosa. The cutaneous manifestations observed were pallid macular eruption of the trunk (21%) and small papular and desquamative lesions (syphilides) of the soles and palms (42%) (Fig 5, B and C) that were also observed on the trunk (50%) and around the mouth (8%) and the genital area (penis, scrotum, and perianal region; 21%).

Anal and genital mucosal involvement consisted essentially of erosive or ulcerative lesions, which were observed in 9 patients (37%). Many patients presented with multiple adenopathies in the inguinal

and cervical areas (42%). One patient initially presented with thrombosis of the dorsal vein of the penis. Two patients received a diagnosis of neuro-ophthalmologic syphilis.

#### **Treatment and outcome**

Most patients were treated with benzathine benzylpenicillin (1 intramuscular injection of 2.4 mIU). The 2 patients with neuro-ophthalmologic involvement received intravenous penicillin G, and 5 patients received a 3-week course of doxycycline because of suspected penicillin allergy. All outcomes reported were favorable, generally within 1 to 2 weeks, but data were missing for 8 patients.

## **DISCUSSION**

#### **Population characteristics and potential biases**

This was a single-center study, and as a result, the population studied presented certain characteristics representative of the epidemiology of syphilis in Paris, France. This probably accounts for the large proportion of men who had sex with men, the age range of the patients, and the large proportion of patients living with HIV.<sup>7</sup>

Because of the retrospective nature of the study and the small number of patients, it is limited by missing data and a lack of statistical power. Nevertheless, it provided certain information of potential clinical utility.

#### **Diagnostic difficulties**

This study shows that syphilis remains difficult to diagnose, even in the presence of clinical symptoms and suggestive epidemiologic data (men who have sex with men, HIV, history of other sexually transmitted diseases, etc). This was particularly true for patients presenting with isolated oral manifestations. These difficulties may be partly due to a lack of awareness among physicians and patients of this particular (but not rare) form of the disease. Oral manifestations can take various and often nonspecific forms. In some cases, the oral lesions were painless (although this information was missing from the files of most of the patients included). In the small case series published to date, asymptomatic oral lesions accounted for almost 50% of cases, often including primary syphilis chancres, which are usually painless.<sup>8</sup> This clinical characteristic may also have contributed to the long time to diagnosis. If painless oral lesions are present, they could help to exclude certain differential diagnoses in which the lesions are usually painful (mouth ulcers, pemphigus, lichen, etc). The times to diagnosis observed for our patients were similar to those reported in previous studies, which ranged



**Fig 5.** Angular mucositis (A) associated with papules of the palms (B) and arms (C).



**Fig 6.** Palatine nodular and erosive lesions.



**Fig 7.** Chronic ulcerative and vegetative lesions of the soft palate.

from 3 weeks to several months.<sup>9-11</sup> However, this finding may also be biased by the publication of cases being driven by diagnostic challenges.

Almost all the patients in our study population were men with a background suggestive of sexual risk factors and a history of sexually transmitted diseases. These elements are probably not always considered by the first physicians consulted by patients. All practitioners encountering patients with oral and dermatologic complaints should assess the existence of sexually transmitted disease risk factors.

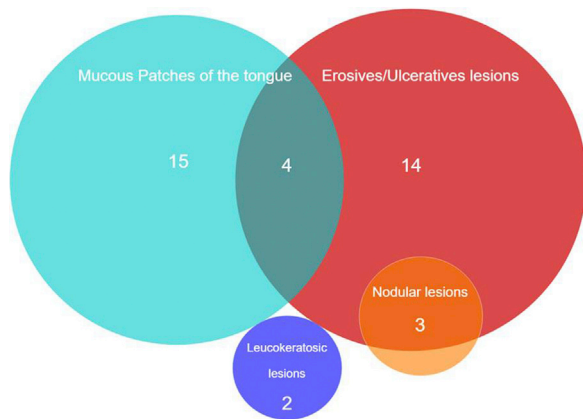
The time to diagnosis was shorter for patients living with HIV despite a frequency of isolated oral lesions similar to that in patients not infected with HIV. This difference may be due to closer follow-up and easier access to specialists in sexually transmitted diseases.

A biopsy was performed on the oral lesions in a large proportion of patients presenting with secondary syphilis without extraoral clinical manifestations. In these patients (who were frequently tobacco smokers), the subacute isolated erosive or ulcerative and sometimes painless lesions found were reasonably suggestive of neoplasia. Clinical course

was always rapidly favorable after antibiotic treatment (generally within 1 to 2 weeks). Rapid serologic testing and closer follow-up would have avoided the need for this unpleasant procedure in most cases. More than half the patients in our study received presumptive treatment for differential diagnoses (proton-pump inhibitors, antibiotics, antihistamines, etc), illustrating the diagnostic difficulties reported in most published cases.<sup>12,13</sup>

### Clinical phenotypes

Syphilis still deserves its historical nickname: “the great imitator.” As illustrated here, its oral manifestations are diverse and often misleading. We identified different phenotypes (Fig 8). Erosive and ulcerative lesions were the most prevalent, consistent with published reports.<sup>8,14</sup> These lesions could be single or multiple, acute or chronic, painless or painful, and isolated or associated with extraoral signs. More rarely, our patients presented with nodular or leukokeratotic lesions, which have been reported less frequently.<sup>5,15</sup> Nodular lesions were observed only in association with erosive or ulcerative lesions, which suggests that they represent



**Fig 8.** Venn diagram presenting the distribution of patients and their clinical phenotypes of oral manifestations.

a certain subtype or a progressive form of erosions or ulcerations. The other main clinical phenotype was mucous patches on the tongue, which are more evocative of syphilis and more frequently observed with extraoral manifestations. These manifestations were mostly skin eruptions suggestive of syphilis and adenopathy. Anal and genital mucosal erosions were frequently involved and were missed by the clinicians initially consulted. The presence of oral lesions should therefore lead to a careful examination of the genital and anal mucosae and a thorough dermatologic examination.

## CONCLUSION

Oral manifestations are frequent in secondary syphilis and are often observed in isolation. These forms can be challenging for clinicians, as demonstrated by the long time to diagnosis. They may have diverse features, such as subacute multiple erosive or ulcerative lesions, nodular or leukokeratotic plaques in some cases, or mucous patches on the tongue (which are more directly suggestive of syphilis). When present, concomitant or past skin eruptions can help to orient the diagnosis, as can associated anal or genital erosions and the existence of sexually transmitted disease risk factors, which are often ignored at the initial consultation.

Diagnosis is generally confirmed by serologic tests, and treatment is generally based on antibiotics. New point-of-care rapid diagnostic tests and molecular biology techniques are gaining ground

in medical practice and will probably facilitate diagnosis and screening.<sup>16</sup> Nevertheless, such tests still require an initial clinical suspicion, based on a knowledge and awareness among clinicians of the many forms of this curable disease.

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